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Brief Clinical Report

Central Precocious Puberty in Klinefelter Syndrome: A Case Report With Longitudinal Follow-Up of Growth Pattern

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We report idiopathic central precocious puberty in a boy with Klinefelter syndrome and describe the pattern of linear growth and body proportion from the onset of precocious puberty to final height. The patient was not treated for precocious puberty. He reached adequate adult height, for both general population and normative values of Klinefelter syndrome and normal body proportions. We conclude that precocious puberty in Klinefelter syndrome may result in normal body proportion by inducing a major growth spurt of the trunk rather than in the limbs, and that adult height prognosis is not altered by precocious puberty. Given the possible occurrence of precocious puberty in Klinefelter syndrome, we advise a karyotype analysis in boys with sexual precocity, mainly in those who show small rather than enlarged testes. © 1996 Wiley-Liss, Inc.

KEY WORDS: Klinefelter syndrome, central precocious puberty, body proportion, linear growth, final height

INTRODUCTION

Klinefelter syndrome occurs to approximately 1:500/1:1,000 males and it is the most common form of male hypogonadism [Grumbach and Conte, 1992]. Before puberty, Klinefelter syndrome is rarely diagnosed because the hypothalamic-pituitary-gonadal axis is quiescent [Grumbach and Conte, 1992]. However, affected individuals may show suggestive minor facial anomalies, micropenis, reduced testicular volume, and/or abnormalities in testicular position [Grumbach and Conte, 1992]. Before puberty, patients have normal height, but they show reduced upper/lower body segment ratio, which represents a main finding in this syndrome [Schibler et al., 1974].

In boys the appearance of secondary sex characteristics before the age of 9 years is considered precocious [Kletter and Kelch, 1993]. If the sexual precocity results from the reactivation of hypothalamic-pituitary-gonadal axis, the condition is called central precocious puberty (CPP) and it may be idiopathic or associated with neurological abnormalities [Kletter and Kelch, 1993]. Increased levels of sex steroids in patients affected by CPP result in an increased skeletal maturation. In this case, growth velocity cannot keep up with it, resulting in short stature in adulthood [Thamdrup, 1961]. CPP has been diagnosed occasionally in patients with Klinefelter syndrome [Chaussain et al., 1980; Grumbach and Conte, 1992; von Muhlendal and Heinrich, 1994].

In this paper, we report the long-term follow-up of one patient with Klinefelter syndrome and CPP, and analyze the pattern of linear growth and body proportion.

CLINICAL REPORT

C.G. is a 7 3/12-year-old white male who was sent to us for precocious puberty. The child was born by vaginal delivery, his birth weight and length were 3,080 g and 51 cm, respectively. At 5 years, his parents noticed the appearance of pubic hair and an increase in penile length.

At our first examination, the patient presented advanced pubertal development and increased height, but he had small testes (Table I). He did not show body disproportion or gynecomastia. Bone age (Greulich and Pyle method [1959]) was 10 6/12 years, and predicted adult height (Bayley-Pinneau method [1952]) in the range of target height [calculated by adding or subtracting 8.5 cm to mid-parental height (measured father's height + mother's height + 12.5 cm/2)] (Table I). Neurological examination was normal. The results of endocrinological investigation are reported in Table II. LH, FSH, and testosterone values were pubertal. Basal and ACTH-stimulated cortisol and 17-hydroxyprogesterone, β-HCG, α-fetoprotein, prolactin, and thyroid hormones were normal for age (Table II). Peripheral lymphocyte chromosome analysis showed a 47,XXY karyotype without apparent mosaicism. Chest roentgenogram and ultrasonography of the adrenal glands

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TABLE I. Growth Data of Patient at First Observation (1st) and at the Final Height (FH)*

	1st	FH
Chronologic age, years	7 3/12	15 5/12
Statural age, years	9 8/12	—
Bone age, years	10 8/12	17 8/12
Height, cm	136.0	176.5
Height, SDS according to CA	2.60	0.85
Height, SDS according to BA	−0.50	0.30
Sitting height, SDS according to CA	3.00	1.00
Sitting height, SDS according to BA	0.50	0.20
Subischeal leg length, SDS according to CA	1.60	0.20
Subischeal leg length, SDS according to BA	−0.70	0.30
Pubertal stage	Ph2/3	Ph5
Testes, ml	4/5	4/4
Testes, SDS according to pubertal stage	−1.40/−1.13	−2.67/−2.67
Paternal height, cm	178.0	—
Maternal height, cm	155.0	—
Mid-parental height, cm	173.0	—
Range target height, cm	185.5/168.5	—
Predicted adult height, cm	179.4	176.5[a]
Predicted adult height, SDS	0.71	0.27[a]
Predicted adult height minus mid-parental height, cm	+6.4	+3.5[b]

* CA, chronologic age; BA, bone age; SDS, standard deviation score (calculated according to the formula: patient value − mean normal value for age and sex/standard deviation of normal mean by using the normative values of Tanner [Tanner et al., 1966; Tanner and Whitehouse, 1978]).
[a] Final height.
[b] Final adult height minus mid-parental height.

and the abdomen were unremarkable. Brain computed tomography and nuclear magnetic resonance was negative.

Since predicted adult height was adequate for target height and in the adult normal range, we proposed to the parents clinical follow-up, but no treatment. The patient was seen every 6 months. There was a normal progression of pubertal development (studied according to Tanner and Whitehouse [1976] only for pubic hair development, because the testicular size is not a valid index of pubertal development in Klinefelter syndrome [Salbenblatt et al., 1985]), but testicular volume did not increase (measured by Prader orchidometer and expressed as standard deviation score according to the normative data of Zachmann et al. [1974]). The patient's growth curve progressed regularly (Fig. 1). At the age of 15 5/12, the patient reached final height (Fig. 1) with normal body proportion (Fig. 2) but reduced testicular volume (Table I). He developed mild rounding of areolae but no true gynecomastia. At this age, testosterone levels were in the low-normal adult range (Table II), while basal and GnRH stimulated levels of LH and

TABLE II. Endocrinological Data of Patient at the First Observation (1st) and at the Final Height

	1st	FH	n.v.[a]
LH basal, IU/L	4.2	16.5	0.5–6.0
LH peak, IU/L[b]	37.5	67.8	7.0–25.0
FSH basal, IU/L	3.2	13.0	1.0–7.0
FSH peak, IU/L[b]	18.7	27.2	2.0–11.0
Testosterone, nmol/L	9.8	10.1	10.0–35.0
Cortisol basal, nmol/L	421.0	487.0	190–600
Cortisol peak, nmol/L[c]	984.5	ND	At least basal × 2
17-hydroxyprogesterone basal, nmol/L	1.6	2.5	1.0–6.0
17-hydroxyprogesterone peak, nmol/L[c]	6.3	ND	<30.0
βHCG, IU/ml	0.1	ND	<5.0
α-fetoprotein, μg/L	2.0	ND	0–20.0
Prolactin, μg/L	7.0	12.0	5.0–15.0
Free thyroxine, pmol/L	17.5	15.4	9.0–27.0
Free triiodiothyronine, pmol/L	7.4	6.4	4.5–9.5
Thyroid stimulating hormone, mU/L	2.1	2.7	0.5–5.0

* ND, not done. Serum levels of LH, FSH, testosterone, cortisol, 17-hydroxyprogesterone, prolactin, thyroxine, triiodiothyronine, thyroid stimulating hormone, βHCG, and α-fetoprotein were measured by commercially available kits. For all measurements, inter-assay variability was less than 9% and intra-assay less than 7%.
[a] Prepubertal n.v.: LH, IU/L: <3.5; LH peak, IU/L: <15.0; FSH basal, IU/L: <4.5; FSH peak, IU/L: <12.0; Testosterone, nmol/L: <2.0; 17-hydroxyprogesterone basal, nmol/L: 0.5–4.0; Prolactin, μg/L: <10.
[b] After intravenous injection of 100 μg GnRH (Lab. Serono, Switzerland).
[c] After intravenous injection of 0.25 mg ACTH (Synacthen, Lab. Ciba, France).

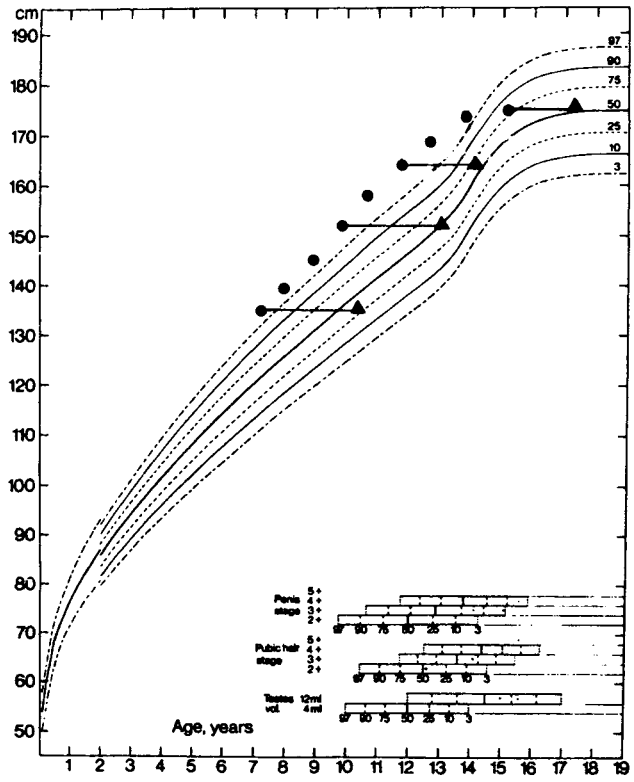

Fig. 1. Growth curve of the patient [● = chronological age; ▲ = bone age].

FSH were above normal (Table II). The other endocrine values were normal (Table II).

Informed consent was obtained from both the parents of proband, and the study was approved by the ethical committee for human investigation of our department.

DISCUSSION

Klinefelter syndrome is the most common cause of primary hypogonadism in males [Grumbach and Conte, 1992]. However, this syndrome is rarely diagnosed in childhood because affected boys show relatively few clinical findings [Grumbach and Conte, 1992; Kletter and Kelch, 1993]. Sometimes, Klinefelter syndrome may be diagnosed in childhood because of precocious sexual development [Dickerman et al., 1977; Chaussain et al., 1980; Castro-Magana et al., 1985]. Recently, von Muhlendahal and Heinrich [1994] reviewed the published cases of sexual precocity in Klinefelter syndrome and underlined that the association of this condition with sexual precocity is too frequent (5.5-fold higher than expected) to be considered a mere coincidence.

The association of Klinefelter syndrome and precocious puberty has been reported in 14 boys [Pierson et al., 1975; Dickerman et al., 1977; Danon et al., 1978; Floret et al., 1979; Chaussain et al., 1980; Castro-Magana et al., 1985; Beasley et al., 1987; Konig et al., 1990; Grumbach and Conte, 1992; von Muhlendahal and Heinrich, 1994; Derenoncourt et al., 1995]. In eight cases, the precocious puberty was peripheral and due to hormonally active malignancies [Pierson et al., 1975; Danon et al., 1978; Floret et al., 1979; Chaussain et al., 1980; Beasley et al., 1987; Konig et al., 1990; Derenoncourt et al., 1995]. In one case a hamartoma of the third ventricle was found [Chaussain et al., 1980]; in the other five patients and in our-own case, CPP was considered "idiopathic."

Idiopathic CPP is diagnosed in a minority of boys, while it is predominant in girls [Bridges et al., 1994]. On the other hand, the available data show that most boys with Klinefelter syndrome and CPP had an idiopathic form [Dickerman et al., 1977; Castro-Magana et al., 1985; Grumbach and Conte, 1992; von Muhlendahal and Heinrich, 1994]. As the occurrence in the onset of puberty was found to occur earlier in Klinefelter syndrome boys than in normal males [Salbenblatt et al., 1985], it could mean that the presence of an extra-X chromosome may predispose some of these patients to a feminized timing in the onset of puberty and to a greater frequency of idiopathic CPP, as in females. This hypothesis is supported by the observation that in Klinefelter syndrome the mean age and the mean intensity of peak height velocity is intermediate between those of normal males and females [Topper et al., 1982].

Before puberty, abnormal body proportion with increased length of the legs and small genitalia are the cardinal physical findings in Klinefelter syndrome [Schibler et al., 1974]. Abnormally long legs are not related to delayed adolescence or endocrine testicular insufficiency [Schibler et al., 1974]. Indeed, delayed puberty is not usually observed in Klinefelter syndrome, and pituitary-gonadal function is relatively normal in prepubertal age and even during puberty almost until pubertal stage 3 [Topper et al., 1982; Salbenblatt et al., 1985]. Therefore, the abnormal body proportion and the

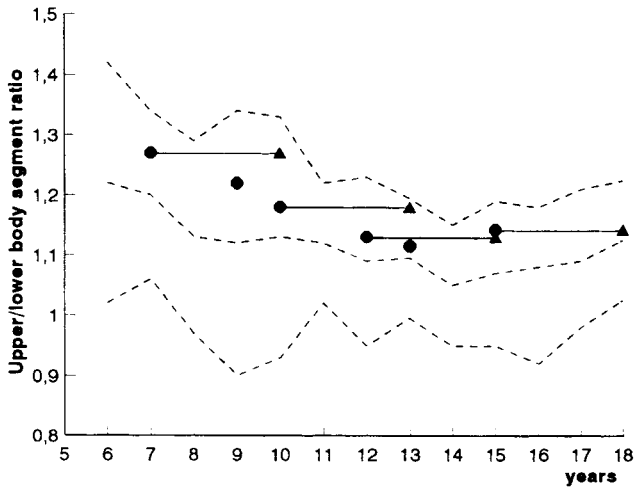

Fig. 2. Pattern of upper/lower body segment ratio of the patient according to his chronological age [●] and bone age [▲]. The broken lines represent normal mean (middle line), +2 standard deviations (upper line) and −2 standard deviations (lower line) (normal values from Arad et al. [1979]).

pattern of linear growth during the prepubertal period are likely due to the phenotypic expression of the chromosomal imbalance [Schibler et al., 1974]. In our case, body disproportion was not evident even in adulthood. It is well known that CPP stimulates growth of the trunk more than that of limbs [Martinez et al., 1984]. Such an effect is particularly marked in boys and it has been related to a direct effect of testosterone on the growth of the spine [Martinez et al., 1984]. Thus, in our patient CPP may have increased growth of the trunk, matching that of limbs and leading to adult normal body proportions.

The goal of treatment in CPP is halting or reversing the decline of height potential [Kletter and Kelch, 1993]. In our patient, predicted height was comparable to target height and, even though he was not treated, his final height (176.5 cm) was in normal range for general population [Tanner et al., 1966] and adequate for genetic potential as well as for patients with Klinefelter syndrome [Schibler et al., 1974]. Our data are comparable with those of other untreated patients with Klinefelter syndrome and CPP who reached final height [Dickerman et al., 1977; von Muhlendahal and Heinrich, 1994]. In fact, such patients reached a mean final height of 182.4 cm (range, 172–189 cm) [Dickerman et al., 1977; von Muhlendahal and Heinrich, 1994], that is normal for Klinefelter syndrome (adult mean, 178.8 cm; range, 167–198 cm [Schibler et al., 1974]).

Testosterone levels in patients with Klinefelter syndrome are within normal range during the first stage of pubertal development; later on, hormone levels do not increase because of the testicular failure, remaining in low-normal range until adulthood [Topper et al., 1982; Salbenblatt et al., 1985]. These low-normal values should permit to reach adequate adult height in spite of precocious sexual development.

Testicular biopsy in a boy with Klinefelter syndrome and CPP showed hyalinized tubules, clumping of Leyding cells, and absence of germ cells, suggesting that precocious stimulation of the testes may lead to premature appearance of typical histological changes of seminiferous tubule dysgenesis [Grumbach and Conte, 1992]. We were unable to perform testicular biopsy in our patient; moreover, the occurrence of fertility in Klinefelter syndrome, albeit rare [Laron et al., 1982], can suggest that there can be no definite prognosis in regard of future fertility when Klinefelter syndrome is diagnosed in childhood [Laron et al., 1982].

In conclusion, CPP in boys with Klinefelter syndrome can lead to normal body proportions, without altering height prognosis. Therefore, treatment does not seem advisable. Since the occurrence of CPP seems to be increased in Klinefelter syndrome, a chromosome analysis is advisable in boys with sexual precocity, who have small rather than enlarged testes.

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